CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 83232

BIOEQUIVALENCE REVIEW(S)

Hydrochlorothiazide Tablets 50 mg.
NDA 83-232

Danbury Pharmacal, Inc.
AF 42-129
Submission dated 3/22/73

REVIEW OF A BIOAVAILABILITY PROTOCOL

1. This is the second protocol submitted for the above drug. The first was written by [redacted] (reviews dated 12/12/72 and 3/1/73). This protocol was designed by [redacted]. It will compare the comparability of the above drug with Merck, Sharp & Dohme's Hydrodiuril.

2. The study will employ 20 normal healthy male volunteers between 21 and 50 years of age. Their weight will be within 10% of that specified in the Metropolitan Life Insurance Co. Bulletin.

3. A CBC, BUN, FBS, SGOT, Serum Alkaline Phosptatase, serum bilirubin, urinalysis (with microscopic) and a differential white count will be conducted on each subject. In addition a Hematocrit and hemglobin should be run if not already included in the CBC.

4. The volunteers will be non-instutionalized subjects. Signed informed consent will be obtained.

5. All subjects are to obstain from other drugs for 7 days and from alcohol for 48 hours prior to test initiation. They should however abstain from other drugs for two weeks prior to test initiation.

6. The reference drug will be Merck, Sharp & Dohme's Hydrodiuril.

7. Both test and reference drugs will be assayed for potency and content uniformity.

8. The study will employ a simple 10 x 10 crossover design. The crossover interval was not specified but should have been. It should occur after 10 half lifes of the drug. We recommend a one week interval.

9. A dose of 50 mg. will be administered with 6 to 8 ounces of water, to 12 hour fasted subjects. Fasting will continue for four hours post dosage. Coffee will be prohibited during the entire study day.

10. The urine collections will occur at 0, 1, 2, 3, 4, 8, 12, and 24 hours [redacted]f water will be ingested 1 hour prior to dose administration and at the time of each urine collection.

11. Urine volume and pH will be determined for each collection period. The samples will be analyzed by the method of Sheppard et. al. will validate the method remitting statistical curves recovery data etc. The standard curves and data used to determine them should also be submitted.

12. An analysis of variance will be done for the rate and amount of drug excreted for each sample collection and the cummulative 24 hour excretion.

13. The study will be conducted in the offices of , at The principal investigator will be curriculum vitae was not furnished.

RECOMMENDATION:

Acceptance of the protocol provided that a curriculum vitae is furnished for the principal investigator, and that points 3, 5, 7, and 11 are adequately complied with.

/S/

Jerome P. Skelly, Ph.D.
Acting Supervisor
Division of Clinical Research

Hydrochlorothiazide Tablets 50 mg.
ANDA 83-232

Danbury Pharmacal, Inc.
AF 42-129
Submission dated 1/30/73

REVIEW OF A PROPOSED BIOAVAILABILITY STUDY

1. This submission responds to the deficiencies noted in DCR's review dated 12/12/72.

2. The clinical phase of the study will be carried out at the office of the
A C.V. was submitted.

3. Only non institutionalized volunteers will be employed in this crossover study. Written informed consent will be obtained.

4. The urinalysis will include a microscopic.

5. Urine collections will be better fractionated. Collections will be 0-1, 1-2, 2-3, 3-4, 4-8, 8-12, 12-24 hours.

6. A standard water load of 200-250 cc will be given one hour before, at time of drug administration, and at the time of each urine collection.

7. The ANOVAR will be performed for the rate and amount of drug excretion for each collection period and for the cumulative 24 hours excretion.

8. The test and reference drugs will be assayed for potency and content uniformity.

9. The assaying laboratory will submit data to demonstrate that the analytical method has the required sensitivity, specificity, and linearity.

RECOMMENDATION:

Approval of the protocol for this proposed bioavailability study.

/S/

Jerome P. Skelly, Ph.D.
Acting Supervisor
Division of Clinical Research

Hydrochlorothiazide Tablets 50 mg
ANDA 83-232

Danbury Pharmacal
Danbury, Connecticut
AF 42-129
Submission Dated:
February 28, 1974

REVIEW OF A BIOAVAILABILITY STUDY

OBJECTIVES:

To compare Danbury's hydrochlorothiazide, 50 mg Tablets to Merck, Sharp and Dohme, Hydro Diuril (hydrochlorothiazide) 50 mg Tablets, by measuring urinary excretion.

SUMMARY:

This proposed protocol for this study was reviewed and accepted by our Division. Twenty-two subjects were used, however because of a mixup in the lab, subjects 3 and 9 were not included in the results. Subjects were adequately screened for medical history of serious disease and clinically tested. They were free from other medication for 7 days. After fasting for 12 hours they received a single dose of hydrochlorothiazide, 50 mg tablet, Danbury Lot 7509 or Hydro-Diuril Merck, Sharp and Dohme 50 mg tablet Lot P2898. Subjects drank of water, one before dosing, the dose, and at each collection time. Urine was collected for 24 hours prior to administrating the drugs, and at 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 8, 8 to 12, and 12 to 24 hours. Volume and pH were measured and each sample was analyzed for hydrochlorothiazide by the method of Sheppard, H. et al, J.A. Pharm. Sci. Ed. Nov. (1960).

Before we can reach a reasonable conclusion, the firm should submit the analysis of variance for the rate and amount of drug excretion for each sample collection period and for the cumulative 24 hour excretion. Raw data should be included. These data were requested in each review of the proposed protocols.

/S/

Joseph J. McGuire
Clinical Research Branch

NDA 83-232
AF 42-129

JUN 0 4 1974

Danbury Pharmacal, Inc.
Attention: Mr. Ira Sacks
131 West Street
Danbury, CT 06810

Gentlemen:

Reference is made to the bioavailability study you submitted for Hydrochlorothiazide Tablets, 50 mg.

The study has been reviewed by our Division of Clinical Research and they have the following comment:

Before we can reach a reasonable conclusion, the firm should submit the analysis of variance for the rate and amount of drug excretion for each sample collection period and for the cumulative 24 hour excretion. Raw data should be included. These data were requested in each review of the proposed protocols.

Sincerely yours,

/S/

Marvin Seife, M.D.
Director
Generic Drug Staff
Office of Scientific Evaluation
Bureau of Drugs

5/3/74

Hydrochlorothiazide
50 mg Tablets
ANDA 83-232

Danbury Pharmacol, Inc.
Danbury, Connecticut
AF #42-129
Submission Dated:
July 23, 1974
July 09, 1974

REVIEW OF A BIOAVAILABILITY STUDY

OBJECTIVES:

To compare the levels of Danbury's Hydrochlorothiazide, 50 mg Tablets in urine to Hydrodiuril, Merck, Sharp and Dohme, 50 mg Tablets.

SUMMARY:

This proposed protocol for this study was reviewed and accepted by our Division. Twenty-two subjects were used, however because of a mix up in the lab, subjects 3 & 9 were not included in the results. Subjects were adequately screened for medical history for serious disease and clinically tested. They were free from other medication for 7 days. After fasting for 12 hours they received a single dose of hydrochlorothiazide, 50 mg tablet, Danbury Lot# 7509 or Hydro-Diuril, Merck, Sharp and Dohme 50 mg tablet Lot P2898. Subjects drank of water, one before dosing, ounces with the dose, and at each collection time. Urine was collected for 24 hours prior to administrating the drugs, and at 0-1, 1-2, 2-3, 3-4, 4-8, 8-12, and 12-24 hours. Volume and pH were measured and each sample was analyzed for hydrochlorothiazide by the method of Sheppard, H., et. al., J. A. Pharm. Sci., Ed. Nov. (1960)

RESULTS:

The results indicate the following:

	CMAX	TMAX	CUMULATIVE (0-24 hours)
Danbury	6.9 mcg/ml	3 hour	5584 mcg
Merck	6.8 mcg/ml	3 hour	5242 mcg

Data was calculated to show the relationship of the two products by dividing the Merck results by Danbury's for each subject. The analysis of variance shows:

	MEANS	VARIANCE	STD. DEV.
Ration Of Volumes	1.13	1.06	1.03
Ratio Of mcg/ml	1.07	0.59	0.77
Ratio Of mcg/sample	1.12	0.83	0.91

RECOMMENDATION:

The data demonstrates that the products are well within experimental error and the products are considered bio-equivalent. The firm should be notified the study is acceptable.

/S/

Joseph J. McGuire
Clinical Research Branch

Hydrochlorothiazide Tablets 50 mg.
ANDA 83-232

Danbury Pharmacal, Inc.
AF 42-129
Submission Sept. 20, 1972

PROPOSED PROTOCOL FOR BIOAVAILABILITY STUDY

1. This proposed protocol is a crossover design comparing Danbury's product hydrochlorothiazide 50 mg. tablet with Merck's Hydrodiuril, Hydrochlorothiazide 50 mg. tablets. The study will be performed by,

The subject will be 20 male adults, between 21-50 years of age and divided into 2 groups of 10. The subjects will be adequately tested for renal, hepatic disease, and blood disorder. The subjects will not take any medication for 7 days prior to the test. The subjects will fast for 12 hours before administration of the drug. They will receive a single dose, one 50 mg. tablet, with of water. No food will be taken for 4 hours after the initial dose, but there will be no restrictions on water. After a seven day interval the groups will be crossedover on the other drug.

A 24 hour urine specimen will be collected prior to dosing. After the initial dose urine samples will be collected at 0-1 hour, 1-3, 3-6, 6-9, 9-12, 12-16, and 16-24 hours.

The urine volume and pH will be measured for each sampling period, and urine assayed for hydrochlorothiazide by the method of Sheppard, H., Mowles, T. F., and Plummer, A. J.; Determinate of Hydrochlorothiazide in urine, J. Am. Pharm. Assoc. Sci., Ed., 1960.

2. The firm should identify the site where the clinical phase will be carried out and a description of the facilities. The principal investigator responsible for conducting the study should be identified.

3. The subjects should be screened for any history of chronic alcohol consumption and if positive they are not eligible. Subjects should give informed consent in writing, and the source of subject revealed.

4. The urine collection should be better fractionated. It is necessary to have frequent collections in order to obtain the slope of the curve. 0-1, 1-2, 2-3, 3-4, 4-8, 8-12, 12-24 hour collections are recommended.

5. It is recommended that a standard water load of be given one hour before, at time of drug administration, and at the time of each urine collection.

6. The urinalysis should include a microscopic examination.

7. The ANOVAR should be done for the rate and amount of drug excretion for each sample collection period and for the cumulative 24 hour excretion.

8. The investigator should be identified and a C. V. obtained.

9. The assay for the drugs should include a content uniformity determination. The batches numbers of both products should be given, and the test drug should be from a production batch, and the size of the batch stated.

10. The firm should submit data to demonstrate that the analytical method has the required specificity, sensitivity and linearity to measure the drug and its metabolites at the levels expected in the clinical specimens. Supporting data such as standard curves and recovery data should be submitted.

RECOMMENDATIONS:

1. We note the firm states the weight range will be in accordance with the attached table, but no table is attached.

2. The firm should submit all of the required information for an abbreviated new drug application. We should notify the firm of the discrepancies in the bioavailability study, as listed in items 2 through 10.

/S/

Joseph J. McGuire
Chemist
Division of Clinical Research